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Interplay between platelets and coagulation: from protective haemostasis to pathological arterial thrombosis

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Comment:

This article provides a comprehensive didactic review on the mechanisms regulating haemostasis and its transition to pathological arterial thrombosis. The authors clearly explain how the body implements a precise system —involving platelets, coagulation factors, and the vascular endothelium— to stop haemorrhages, and how these very mechanisms can turn harmful in the context of atherosclerosis.

The text highlights the central role of the healthy endothelium as a haemostatic balance regulator, as well as the role of protective molecules such as nitric oxide, prostacyclin, and differentnatural coagulation inhibitors. The factors altering this balance are also discussed, such as endothelial dysfunction, chronic inflammation, and the increase of hyperreactive platelets.

A particularly interesting aspect is the approach on emerging risk factors, such as lipoprotein(a), clonal haematopoiesis, and subclinical inflammation, contributing to a prothrombotic state even in people with no apparent clinical condition. In this context, the authors highlight the importance of subclinical atherosclerosis early detection, based on the findings of the PESA study, which shows how many apparently healthy people already present signs of a vascular condition.

As for treatment-related implications, the need to develop treatments preventing thrombosis without compromising physiological haemostasis is underlined. Some promising targets are suggested, including factor XI/XIa and platelet receptor GPVI, which when inhibited may offer antithrombotic protection with a lower risk of bleeding.

In summary, this is a highly recommended article on account of its clarity, depth, and up-to-date approach. It is valuable both in terms of pathophysiological knowledge and the development of preventive treatment strategies in the cardiovascular field.

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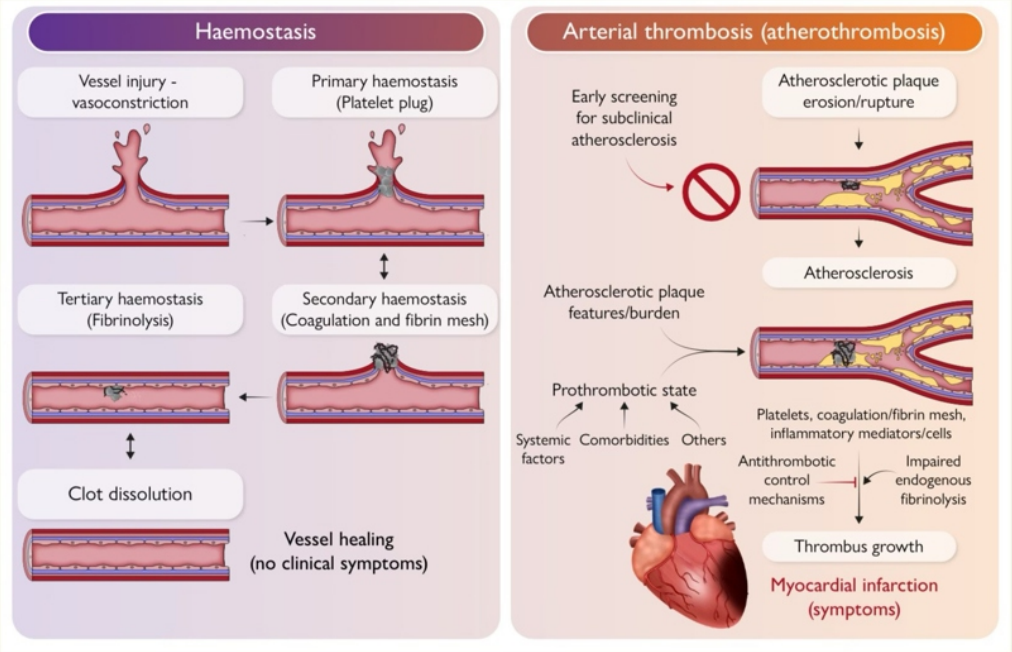
Graphical Abstract



Different mechanisms that govern haemostasis and arterial thrombosis. Haemostasis is the physiological process responsible for repairing vessel injuries and preventing bleeding. It involves four major, interconnected stages: local vasoconstriction; primary haemostasis, where a platelet plug is formed; secondary haemostasis, which involves the activation of the coagulation cascade and the formation of a fibrin clot; and tertiary haemostasis, characterized by fibrinolysis, the process that breaks down the fibrin clot. In contrast, atherothrombosis is a condition characterized by the formation of a platelet-rich thrombus in response to an atherosclerotic plaque disruption. This process involves coagulation factors and the recruitment of inflammatory cells, contributing to thrombus progression and further cardiovascular complications.

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Effect of early administration of fibrinogen replacement therapy in traumatic haemorrhage: a systematic review and meta-analysis of randomised controlled trials with narrative synthesis of observational studies

Tom Burt, Ashley Guilliam, Elaine Cole, Ross Davenport

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Author of the comment: *Dra. Raquel Ferrandis Comes.* *Anaesthesiology and Reanimation. Hospital Universitari i Politècnic La Fe, Valencia. Member of the SEDAR-COVID working group.*

The authors present a systematic review of the literature aimed at assessing the efficacy of early administration of fibrinogen. The first piece of data that stands out is that, of the 1906 studies selected, only 12 are included, 5 of which are randomised clinical trials, 3 with fibrinogen concentrate and 2 with cryoprecipitate. Hence, the first conclusion is that further studies are required, particularly to validate the empirical administration versus the goal-directed one.

It must be noted that the authors mention a "bias" risk in 6 of the 7 observational studies considered, including very heterogeneous patients, as befits a real-life trauma patient. Similarly, clinical studies also present confusion factors, such as issues with blinding or patient randomisation. All in all, a study on patients with multiple traumas does not only involve patients with multiple factors and determinants, but also a "hard to control" clinical scenario.

With all the limitations emerging from the search result, the study does not find a better clinical result with the early administration of fibrinogen, as was not found either in the CRYOSTAT-2 study. This means that a decrease has not been found in terms of mortality, transfusion requirements, or incidence of vein thrombosis. Furthermore, this review does not find any differences between the administration of concentrate and cryoprecipitate, pending the results of the FIESTY II study.

All in all, the management of trauma-caused coagulopathy, which should be early and effective, does not have yet the scientific evidence we would like to see.

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Prothrombin Complex Concentrate vs Frozen Plasma for Coagulopathic Bleeding in Cardiac Surgery: The FARES-II Multicenter Randomized Clinical Trial

Keyvan Karkouti, Jeannie L Callum, Justyna Bartoszko, Kenichi A Tanaka, Sigurd Knaub, Sukhpal Brar, Kamrouz Ghadimi, Antoine Rochon, Darren Mullane, Etienne J Couture, Yulia Lin, Christopher Harle, Michelle Zeller, Diem T T Tran, Cristina Solomon, Vivek Rao, Michael Law, Amir L Butt, Edward P Chen, Maria Rosal Martins, Tarit Saha, Andrew W Shih, Marie-Claude Vézina, Fuad Moussa, Raffael Pereira Cezar Zamper, Summer Syed, Hakan Buyukdere, Sylvia Werner, Deep Grewal, Daniel Wong, Kofi B Vandyck, Robert Tanzola, Bevan Hughes, Olivier Royer, Sophia Wong, Jerrold H Levy; FARES-II Study Group

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Author of the comment: *Dra. Pilar Marcos.* *Intensive Medicine. Hospital Germans Trias i Pujol, Badalona, Barcelona.*

Up to 15% of patients undergoing **heart surgery** may present **excessive perioperative bleeding,** which entails an increase in their morbidity and mortality. In order to improve the outcomes of these patients, an **unblinded multi-centre (12 hospitals in Canada and the US) randomized clinical trial (RCT)** was conducted, which we comment here.

The **main endpoint** of the RCT was to prove that treating perioperative bleeding in heart surgery with the administration of **prothrombin complex concentrate (PCC) was not inferior to treating it with fresh frozen plasma (FFP),** as measured by the haemostatic response. This **haemostatic response** was defined as the need for reoperation between 60 min and 24 hours after the administration of the treatment.

Inclusion criteria.

- Age ≥ 18.
- Informed consent, pre-surgery in the US and post-surgery in Canada.
- Heart surgery of any kind, except for heart transplant and type-A aortic dissection.
- Scheduled elective surgery.
- Preferably, an INR ≥ 1.5 was required for randomization, but cases where the bleeding was so critical that there was no time to find out the INR were also accepted. Some centres used the viscoelastic test, but the inclusion criterion was still INR ≥ 1.5.
- Moderate and/or major bleeding in the operation room (before closing) defined by the Lewis et al [1] scale, which is highly surgery-focused.

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Degree	Visual presentation	Anatomic appearance	Visual estimated bleeding ratio (mL/min)	Qualitative description
0	No bleeding	No bleeding	≤ 1	No bleeding
1	Oozing or Intermittent bleeding	Capillary-type bleeding	>1-5	Mild
2	Continuous bleeding	Venule or arteriole bleeding	>5-10	Moderate
3	Controllable jet and/or uncontainable bleeding	Non-central venous o arterial bleeding	>10-50	Severe
4	Unidentified or inaccessible jet	Central venous o arterial bleeding	>50	Critical

Table 1. Lewis et al scale to measure operative bleeding [1]

Intervention. PCC or FFP, based on weight, summarized in Figure 1.

Results. As we can see in Figure 1, the groups were comparable, and in the PCC group, the effective haemostatic response was significantly higher, significant savings in transfusions were observed, and the development of acute kidney failure was significantly lower.

Post-CEC moderate/severe bleeding in heart surgery
11/30/2022 – 5/28/2024

	PCC ≤ 60 Kg: 1500 UI >60 Kg: 2000 UI (n=213)	FFP ≤ 60 Kg: 3 U > 60 Kg: 4 U (n=207)	
Complex surgery	67.6%	73.4%	pns
Emergency surgery	16.9%	21.3%	pns
CEC time (min)	171 DS 76.4	176 DS 80.5	pns
Tranexamic acid dose (g)	3.4 DS 1.6	3.6 DS 4	pns
Heparin dose (UI)	50 343 DS 20 288	51 114 DS 21 474	pns
Protamine dose (mg)	381 DS 116	390 DS 152	pns
Received fibrinogen	42.7%	46.9%	pns
Effective haemostatic response	77.9%	60.4%	p<0.001
Total dose of transfused blood products (Units)	6.6 (5.9-7.5)	13.8 (12.3-15.5)	p<0.001
Thromboembolic events	8.5%	7.2%	pns
Acute kidney failure	10.3%	18.8%	p=0.02

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Comments

- **Informed consent** was obtained before surgery in the US and after surgery in Canada. In Spain, it would be virtually unthinkable to perform an operation with no previous consent. A total of 46 patients, after having been randomized and treated, were excluded from the analysis because they subsequently revoked their consent. Those 46 non-analysed yet treated patients may already account for a significant bias.
- The fact that there was no **common transfusion protocol** to all sites may introduce a very significant bias, even though the amount of tranexamic acid, heparin, and protamine, as well as the number of patients receiving fibrinogen, was similar in both groups. It must also be noted that we have no information on the amount of fibrinogen received by each group. An adequate replacement of fibrinogen may often lead to a lesser need to administer PCC.
- The use of a viscoelastic test was valid in this RCT, but if it was used, an INR ≥ 1.5 was still necessary for patient inclusion. I believe it is currently unthinkable to assess the administration of PCC or FFP in heart surgery without following the transfusion algorithms of a viscoelastic test, as recommended by European guidelines EACTAIC (European Association of Cardiothoracic Anaesthesiology and Intensive Care), EACTS (European Association for Cardio-Thoracic Surgery), and EBCP (European Board of Cardiovascular Perfusion), with a 1A evidence level [(2)]. Taking into account this is an American-Canadian study, upon review of the latest International Consensus Statement, with a strong participation by the US, we can see that this RCT would not make much sense, because this Consensus recommends guiding transfusion using algorithms based on viscoelastic tests because they may reduce bleeding, transfusion, and reoperation, since they can help identifying the underlying cause for the bleeding [(3)]. I believe there is enough evidence as to administer PCC at the time indicated by the viscoelastic test algorithm.

Conclusion. I believe we should administer PCC instead of FFP in cases of bleeding in heart surgery, since the haemostatic action of PCC is superior to that of FFP, and for the first time, an RCT proves that it does not increase the risk of thrombosis. However, the time of administration should be guided by the viscoelastic test.

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